FINAL ACTION

Claim Amendments and Interview Summary

1. As noted in the attached Interview Summary, the examiner contacted Applicant on 18 June 2008 because a set of amended claims and a supplemental set of amended claims were both submitted on 13 March 2008. The supplemental set of claims had been separated by the cover sheet. Hence, the examiner did not know which set of claims was the supplemental set. Applicant's representative informed the examiner that the supplemental set of claims to be examined is the set that has struck-through the phrase "of a liquid material" in line 13 of claim 1.

2. It Is further noted that in the instant amendments to the claims, claims 90, 102-106, and 111 have deleted the word “whereby” and replaced it with the word “wherein” in line 1 of the claims, while claims 89, 91-96, 99-100, 107-110, 117-120, 122-125, and 128-129 have not replaced the word "whereby” with "wherein." IN addition, new claims 134-135 and 140 recite the word “whereby” in line 1. This is merely noted for Applicant's reference and convenience.

Status of the Claims

3. This action is in response to papers filed 13 March 2008 in which claims 87-88, 90-91, 96-98, 102-106, 111-114, 116, 118, 122-123, and 125-126 were amended, no claims were canceled, and new claims 130-140 were added. All of the amendments have been thoroughly reviewed and entered.

The objections to the claims listed in the previous Office Action are withdrawn in view of the amendments.

The previous rejections under 35 U.S.C. 112, second paragraph, are withdrawn in view of the amendments.

The previous rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) not reiterated below are withdrawn in view of the amendments. Applicant's arguments have been thoroughly reviewed and are addressed following the rejections necessitated by the amendments.

Claims 87-140 are under prosecution.

4. The following are new rejections necessitated by the amendments.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 87-88 , 92-93, 97-100, 107, 109, 112-113, 115, 117-118, 120-129, 137, and 140 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,451, issued 27 June 1995) in view of Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002).

Regarding claim 87, Lea et al teach a method for assessing at least one quality or quantity parameter of a particle in a liquid material. In a single exemplary embodiment, Lea et al teach a liquid material (i.e., fluid) comprising particles (column 2, lines 19-35). The particles are blood cells (column 4, lines 25-45). Page 9 of the instant specification recites blood cells as a preferred form of particle. Thus, the blood cells of Lea et al are particles that have bound thereto or comprised therein less that $1x10^6$ analyte detectable positions per particle, and the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding “analytes in an amount of less than $1x10^6$ analyte detectable positions per particle ” (*In re Hyatt*, 211 F.3d1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) (see MPEP 2111 [R-1]). The particles are bound to reagents in the form of superparamagnetic beads (i.e., particles), which selectively and directly bind an analyte position of

said species of analyte because the magnetic beads are attached to selected cells by specific monoclonal antibodies (column 4, line 25-column 5, line 5). The antibodies are a first targeting species. The beads are also attached via direct coupling to a fluorescent labeling agent via a sandwich complex (column 4, line 25-column 5, line 5). Fluorescent labels absorb and emit electromagnetic radiation in the form of light to generate a detectable electromagnetic signal. The fluid containing the particles is then passed through an optical cell (column 2, lines 19-67), which is a sample compartment having a wall part defining an exposing area wherein electromagnetic signals from the sample pass through the wall to the exterior; namely, Figure 1 shows the cell , which is made of optical quality material, allows light to pass through (column 5, lines 9-40). The light that passes through the wall part is then exposed onto an array of detection elements in the form of a CCD array (column 5, lines 9-40). Lea et al also teach a linear dimension of the image on the array to the original linear dimension image is smaller than 20:1; namely, the image is of the particles is magnified in the range of 2 to 15 (column 2, lines 50-60). Because the entire image is magnified less than 20:1, each linear dimension of the image is magnified less than 20:1. The representation is detected as intensities by individual active detection elements; namely, each CCD in the array provides a picture of the particles (column 2, line 50-column 3, line 37). The intensities are processed in order to separate the particle signals from the background; namely, contrast between the particle images and the background is maximized (column 3, lines 50-67), and at least

one quality or quantity parameter is obtained from the processing; namely, the cells are counted (column 3, lines 65-68).

Lea et al also teach that the particle stream speed should be controlled if the stream is moving too fast for accurate counting (column 3, lines 20-30). However, Lea et al do not specifically teach the stream is at a standstill during the exposure of the signals onto the array of detectors.

However, Hansen et al teach a method wherein biological particles in a volume of liquid analyte material are assessed (paragraph 0001), wherein the particles and sample are detected at a standstill during the exposure (paragraph 0070), which has the added advantage of allowing the detection of any weak signals which might indicate the presence of a particle (paragraph 0051). Thus, Hansen et al teach the known technique of having a fluid stream at a standstill during the exposure of the signals onto the array of detectors.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method of Lea et al wherein particle stream speed should be controlled if the stream is moving too fast for accurate counting as suggested by Lea et al so that particle stream speed is controlled to a standstill during the exposure of the signals onto the array of detectors as taught by Hansen et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of improved sensitivity as a result of allowing the detection of any weak signals which might indicate the

presence of a particle as explicitly taught by Hansen et al (paragraph 0051). In addition, it would have been obvious to the ordinary artisan that the known technique of controlling the particle stream speed to a standstill during the exposure of the signals onto the array of detectors as taught by Hansen et al could have been applied to the method having controlled particle stream speed as taught by Lea et al with predictable results because the known technique of controlling the particle stream speed to a standstill during the exposure of the signals onto the array of detectors as taught by Hansen et al predictably results in improved sensitivity of detection.

Regarding claim 88, the method of claim 87 is discussed above. Lea et al teach the particle is a cell; namely, a blood cell (column 4, lines 25-45).

Regarding claim 92-93, the method of claim 88 is discussed above. Hansen et al teach binding a fluorochrome to DNA (i.e., the analyte) within a somatic cell (i.e., claim 92; paragraph 0143). DNA in a somatic cell is inside the nucleus, which is an organelle (i.e., claim 93). Thus, modification of the method of Lea et al in view of Hansen results in a method wherein DNA sequences within the nucleus, which is an organelle, are detected within a cell.

Regarding claims 97-98, the method of claim 87 is discussed above. Lea et al teach also the cells are blood cells (i.e., claim 99; column 4, lines 25-45); blood cells encompass mammalian cells (i.e., claim 97).

Regarding claim 99, the method of claim 87 is discussed above. Lea et al further teach the liquid material comprises at least two different species of particles; namely, the sample comprises biological cells and cells other than

those of interest (column 4, line 25-column 5, line 5). The cells are particles and the cells other than those of interest are at least one additional species of particles in addition to the biological cells, which are a first species of particles.

Regarding claim 100, the method of claim 99 is discussed above. Lea et al teach only one of the species of particles has bound thereto or comprised therein the species of analyte; namely, the particles of interest are bound to reagents in the form of superparamagnetic beads (i.e., particles), which selectively and directly bind an analyte position of said species of analyte because the magnetic beads are attached to selected cells by specific monoclonal antibodies (column 4, line 25-column 5, line 5). Because antibodies are highly specific, the antibodies bind only to one type of cell (i.e., particle) in the sample; namely, only to the cells having the analyte to which the antibodies bind.

Regarding claim 107, the method of claim 87 is discussed above. Lea et al also teach the at least one species of analyte is a medical marker of disease; namely, the counted cells are used to diagnose diseases (column 4, lines 25-40).

Regarding claim 109, the method of claim 87 is discussed above. Lea et al further teach the targeting species is an antibody to the analyte species; namely, the targeting species is the monoclonal antibody on the magnetic bead (column 4, line 25-column 5, line 5).

Regarding claims 112 and 137, the method of claim 87 is discussed above. Lea et al teach the liquid material is a bodily fluid; namely, a blood sample (column 4, lines 25-40).

Regarding claim 113, the method of claim 87 is discussed above. Lea et al also teach the reagent material is an antibody labeled with a reactive moiety; namely, the reagent material is the bead having the antibody thereon, which is then reagent with an optical label in the form of a fluorescent dye (column 4, line 25-column 4, line 5). Because the dye reacts with the antibody/bead, the antibody is labeled with a reactive moiety; i.e., the group that reacts with the dye.

Regarding claim 115, the method of claim 87 is discussed above. Lea et al also teach the addition of lysing agents (column 4, lines 55-65). While Lea et al do not teach the lysing agents are added with the targeting species/labeling agent as part of the reagent material, the courts have held that selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results (*In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946). See MPEP 2144.04 IV.C.

Regarding claims 117-118, the method of claim 87 is discussed above. Lea et al also teach the labeling agent is acridine orange; namely, the beads are also attached via direct coupling to a fluorescent labeling agent, which is a dye, via a sandwich complex (column 4, line 25-column 5, line 5), wherein the fluorescent dye is acridine orange (column 5, lines 34-36).

Regarding claims 120-121, the method of claim 87 is discussed above. Lea et al further teach the image is recorded using an array of detection devices; namely, the recording is made with a CCD array (column 5, lines 9-40).

Regarding claims 122-123 and 140, the method of claim 87 is discussed above.

It is noted that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories,* 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). See also *Upsher-Smith Labs. v. Pamlab, LLC*, 412 F.3d 1319, 1323, 75 USPQ2d 1213, 1215 (Fed. Cir. 2005)(reference disclosing optional inclusion of a particular component teaches compositions that both do and do not contain that component); Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (The court held that the prior art anticipated the claims even though it taught away from the claimed invention. "The fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed."). Thus, the teaching of Lea et al that the flat image **may** be magnified encompasses the alternate embodiment wherein the image is **not** magnified (i.e., claim 122). See MPEP § 2123 [R-5]. A non-magnified image would have an enlargement ratio of 1 (i.e., claim 123). Because none of the linear dimensions are enlarged, the ratio of all of the linear dimensions of the image relative to the exposing domains equal 1, which is less than 4 (i.e., claim 140).

Regarding claim 124, the method of claim 87 is discussed above.

Hansen et al teach the method comprises gathering sufficient information in one exposure (paragraph 0026). Thus, modification of the method of Lea et al with the teachings of Hansen et al results in a method wherein the image is recorded in one exposure.

Regarding claim 125, the method of claim 87 is discussed above.

Hansen et al teach the method comprises gathering sufficient information in more than one exposure (paragraph 0026). Thus, modification of the method of Lea et al with the teachings of Hansen et al results in a method wherein the image is recorded in more than one exposure (i.e., claim 125).

Regarding claim 126, the method of claim 125 is discussed above. Lea et al also teach the assessment of the number of particles is obtained on the basis of more than four images; namely, the images are sampled as ten freeze frame pictures, which are used to assess the number of particles by identifying the number of illuminated objects (i.e., particles; column 5, lines 54-67).

Regarding claim 127, the method of claim 125 is discussed above. Lea et al further teach information about the changes in the image in course of time is used in the assessment of the number of particles; namely, the freeze frame images provide real time information about the number of illuminated objects (i.e., particles; column 5, lines 54-67).

Regarding claim 128, the method of claim 87 is discussed above.

Lea et al do not explicitly teach a distinction between at least two spectral properties of a labeling agent is used to obtain at least one quality or quantity parameter of the particles as an embodiment of the invention of Lea et al.

However, Lea et al do teach a method wherein a distinction between at least two spectral properties of a labeling agent is used to obtain at least one quality or quantity parameter of the particles; namely, the spectral properties of light scattering and fluorescence of the particles are measured, which has the

added advantage of providing information on the surface structure of the particles (i.e., cells) as well as provide information about the fluorescent labels themselves (column 1, lines 30-41).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on cells (i.e., microparticles) as taught by Lea et al in view of Hansen et al so that the method uses at least two spectral properties of a labeling agent to obtain at least one quality or quantity parameter of the particles as taught by Lea et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of providing information on the surface structure of the particles as well as provide information about the fluorescent labels themselves as explicitly taught by Lea et al (column 1, lines 30-41).

Regarding claim 129, the method of claim 87 is discussed above. Lea et al teach the recording of the image comprises exposing a first surface of the sample directly with excitation light from a first light means having a first light source; namely, Lea et al teach Figure 1, which shows excitation light from ultraviolet light source 2, which is a light means having a light source, entering cell 1 through a side wall and thereby directly striking a first surface of the sample, which is the collection of particles within cell 1. Lea et al further teach the particles then fluoresce (Abstract), and the fluorescence signal travels from

the cell through lens 3, which is a focusing means (column 5, lines 5-55). Light from lens 3 then passes to CCD array 5, which is a first detection means comprising at leas a first detector (column 5, lines 5-55 and Figure 1).

8. Claims 89-90 and 95-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) as applied to claim 87 above, and further in view of Griffiths (U.S. Patent Application Publication No. US 2002/0119459 A1, published 29 August 2002).

Regarding claims 89, 90, and 95-96, the method of claim 87 is discussed above in Section 7.

Lea et al do not teach the particles is a bead (i.e., claim 89) to which a nucleic acid is bound (i.e., claim 90) having between 500 and 50,000 analyte detectable positions (i.e., claim 96), which is less than $5x10^5$ analyte detectable positions (i.e., claim 95).

However, Griffiths teaches detection of analyte molecules in the form of DNA molecules (i.e., claim 90) wherein the analyte is bound to a bead (i.e., claim 89; paragraph 0023). Griffiths also teaches the labeling of the DNA molecules (i.e., genetic elements) with fluorescent markers (paragraph 0206), and further teaches detection of as little as a few hundred fluorescent molecules per bead (paragraph 0204). Griffiths also teach detection of labeled nucleic acid molecules allows sorting of the labeled molecules (paragraph 0202), which has

the added advantage of allowing isolation of the specific genetic element having a desired activity (paragraph 0023). Thus, Griffiths teaches the known techniques of detecting particles in the form of beads (i.e., claim 89), wherein the analyte is a DNA molecule (i.e., claim 90), and the particles have a few hundred labeled molecules thereon (i.e., claim 95).

It is noted that the courts have stated where the claimed ranges “overlap or lie inside the ranged disclosed by the prior art” and even when the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have similar properties, a *prima facie* case of obviousness exists (see *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990); *Titanium Metals Corp. of America v. Banner*, 778 F2d 775. 227 USPQ 773 (Fed. Cir. 1985) (see MPEP 2144.05.01). Therefore, the claimed range of between 500 and 50,000 analyte detectable positions (i.e., claim 96) is an obvious variant of the few hundred detectable positions of Griffiths.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the detection of labeled particles as taught by Lea et al in view of Hansen et al so that the method detects particles in the form of beads (i.e., claim 89), wherein the analyte is a DNA molecule (i.e., claim 90), and the particles have a few hundred labeled molecules thereon (i.e., claims 95-96) to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said

modification would have resulted in a method having the added advantage of allowing isolation of the specific genetic element having a desired activity as a result of allowing sorting as explicitly taught by Griffiths (paragraph 0202 and 0023). In addition, it would have been obvious to the ordinary artisan that the known technique of using the beads having a few hundred labeled DNA analytes thereon as taught by Griffiths could have been applied to the method of Lea et al in view of Hansen et al with predictable results because the known technique of using the beads having a few hundred labeled DNA analytes thereon as taught by Griffiths predictably results in reliable detection of genetic samples.

9. Claims 91, 102, 107, and 130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) as applied to claims 87-88 above, and further in view of Baer et al (U.S. Patent No. 5,547,849, issued 20 August 1996).

It is noted that while claim 107 has been broadly rejected as described above in Section 7, the claim is also obvious using the alternative interpretation outlined below.

Regarding claims 91, 102, 107, and 130, the method of claims 87-88 is discussed above in Section 7.

Neither Lea et al nor Hansen et al teach the analyte is a cell receptor bound to a cell membrane (i.e., claim 91). CD4 is a cell receptor bound to a cell

membrane (i.e., claim 130), which is a cluster of differentiation marker (i.e., claim 102) for the disease AIDS (i.e., claim 107).

However, Baer et al teach the detection of leukocytes having CD4 on their surface, which has the added advantage of determining the progression of AIDS (column 8, lines 15-50). Thus, Baer et al teach the known technique of detecting the cell membrane receptor CD4.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on cells (i.e., particles) as taught by Lea et al in view of Hansen et al so that the cell is detection via detection of the cell receptor CD4 (i.e., claim 102), which is a cell receptor bound to a cell membrane (i.e., claim 91) and is a cluster of differentiation marker (i.e., claim 130) for a disease (i.e., claim 107), to arrive at the instantly claimed method as taught by Baer et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of determining the progression of AIDS as explicitly taught by Baer et al (column 8, lines 15-50). In addition, it would have been obvious to the ordinary artisan that the known technique of detection of the cell receptor CD4 as taught by Baer et al could have been applied to the method of Lea et al in view of Hansen et al with predictable results because the known technique of detection of the cell receptor CD4 as taught by Baer et al predictably results in reliable detection of AIDS related samples.

10. Claims 92-93, 103, 110-111, and 114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) as applied to claims 87-88 above, and further in view of Singer et al (U.S. Patent No. 5,728,527, issued 17 March 1998).

It is noted that while claims 92-93 have been broadly rejected as described above in Section 7, the claims are also obvious using the alternative interpretation outlined below.

Regarding claims 92-93, 103, 110-111, and 114, the method of claims 87-88 is discussed above in Section 7.

While Hansen et al teaches binding a fluorochrome to DNA within a cell (paragraph 0143), neither Lea et al nor Hansen et al specifically teach the analyte is a chromosomal DNA sequence (i.e., claim 103) comprised in a cell (i.e., claim 92), or that the reagent material comprises labeled nucleotide probes (i.e., claim 114). Chromosomal DNA sequences within a cell are inside the nucleus, which is an organelle (i.e., claim 93). Probes that bind chromosomal DNA sequences within a cell are in situ hybridization probes (i.e., claim 111), and are a targeting species that is a nucleotide probe complementary to a sequence of an analyte species (i.e., claim 110).

However, Singer et al teach in situ hybridization probes (i.e., claim 111), which bind to specific sequences on chromosomal DNA (i.e., claim 103; column 2, lines 19-45) and are nucleotide probes complementary to a sequence of an analyte species (i.e., claim 110). Chromosomal DNA sequences are inside the

nucleus, which is an organelle (i.e., claim 93), and are thus comprised inside a cell (i.e., claim 92). The oligonucleotide probes are fluorescently labeled (column 1, lines 50-67). Singer et al further teach in situ hybridization probes have the added advantage of determining the expression level of genes during specific developmental stages (i.e., larval and embryonic stages; column 2, lines 19-45). Thus, Singer et al teach the known technique of detection chromosomal DNA within an organelle that is within a cell using in situ hybridization probes.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on cells (i.e., microparticles) as taught by Lea et al in view of Hansen et al so that the detection is of chromosomal DNA sequences using in situ hybridization probes as taught by Singer et al to arrive at the instantly claimed invention with a reasonable expectation of success. The modification would result in a method using in situ hybridization probes (i.e., claim 111), which are a targeting species that is a nucleotide probe complementary to a sequence of an analyte species (i.e., claim 110) and is fluorescently labeled (i.e., claim 114), to bind to specific sequences on chromosomal DNA (i.e., claim 103), which are inside an organelle in the form of the nucleus of the cell (i.e., claim 93), and are thus comprised inside a cell (i.e., claim 92). The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of allowing determination of the expression level of genes during specific developmental stages as explicitly taught by Singer et al (column

2, lines 19-45). In addition, it would have been obvious to the ordinary artisan that the known technique of using the in situ hybridization probes as taught by Singer et al could have been applied to the method of Lea et al in view of Hansen et al with predictable results because the known technique of using the in situ hybridization probes as taught by Singer et al predictably results in reliable detection of sequences within cellular analytes.

11. Claims 92 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) as applied to claims 87-88 above, and further in view of Connors et al (U.S. Patent No. 5,726,009, issued 10 March 1998).

It is noted that while claim 92 has been broadly rejected as described above in Sections 7 and 10, the claim is also obvious using the alternative interpretation outlined below.

Regarding claims 92 and 94, the method of claims 87-88 is discussed above in Section 7.

Neither Lea et al nor Hansen et al teach the analyte is on the surface of an organelle (i.e., claim 94); organelles are inside the cell (i.e., claim 92).

However, Connors et al teach the detection of an analyte on the surface of an organelle; namely, a targeting species/labeling agent in the form of a dye binds to the nuclear membrane. The nuclear membrane is the surface of the nucleus, which is an organelle and is comprised in a cell (i.e., claim 92; column 6,

lines 9-30). Thus, the analyte is the nuclear membrane, which is located on the surface of the organelle (i.e., claim 94). Connors et al also teach the detection of the nuclear membrane (i.e., as an analyte) has the added advantage of identifying dead cells, thereby allowing determination of the number of viable cells in a population (column 6, lines 9-30). Thus, Connors teaches the known technique of detecting an analyte on the surface of an organelle.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on cells (i.e., microparticles) as taught by Lea et al in view of Hansen et al so that the analyte detected in and analyte on the surface of an organelle as taught by Connors et al with a reasonable expectation of success. The modification would result in a method that detects the nuclear membrane, which is on the surface of an organelle (i.e., claim 94) which is comprised inside a cell (i.e., claim 92). The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of allowing determination of the number of viable cells in a population by identifying dead cells as explicitly taught by Connors et al (column 6, lines 9-30). In addition, it would have been obvious to the ordinary artisan that the known technique of detecting an analyte on the surface of an organelle in a cell as taught by Connors et al could have been applied to the method of Lea et al in view of Hansen et al with predictable results because the known technique of detecting an analyte on the surface of an

organelle in a cell as taught by Connors et al predictably results in reliable detection of analytes within cells.

12. Claims 101, 108, and 110 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) as applied to claims 87-88 above, and further in view of Singer et al (U.S. Patent No. 5,728,527, issued 17 March 1998).

It is also noted that while claim 110 has been broadly rejected as described above in Section 10, the claim is also obvious using the alternative interpretation outlined below.

Regarding claims 101, 108, and 110, teach the method of claim 87 is discussed above in Section 7.

Lea et al also teach the simultaneous counting (i.e., detection) of more than one population of cells (i.e., analytes) simultaneously using different colors (column 3, lines 38-50).

Neither Lea et al nor Hansen et al explicitly teach the two distinct populations are bound by two distinct targeting species using two distinct colored labels; i.e., multiplex detection (i.e., claims 101 and 108), nor do Lea et al or Hansen et al teach the targeting species is a nucleotide probe complementary to a sequence of an analyte species (i.e., claim 110).

However, Singer et al teach the targeting of at least two distinct species of analyte; namely, more than one target material is targeted using reagent material

comprising multiple microparticles each having a different target complement, which is a distinct targeting species (i.e., claim 108), and having a difference fluorescent labeling agent (i.e., claim 101; column 16, lines 54-65). The target complements are nucleotide probes complementary to a sequence of an analyte species (i.e., claim 110; column 15, lines 50-67), which has the added advantage of allowing simultaneous analysis of different genes (column 18, lines 1-22). Thus, Singer et al teach the known technique of using two distinctly colored labels.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on cells (i.e., microparticles) as taught by Lea et al in view of Hansen et al so that the detection is multiplex detection using two different colored labels as taught by Singer et al to arrive at the instantly claimed method with a reasonable expectation of success. The modification would result in two distinct populations bound by two distinct targeting species using two distinct colored labels (i.e., claims 101 and 108) using a nucleotide probe complementary to a sequence of an analyte species (i.e., claim 110). The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of allowing simultaneous analysis of different genes as explicitly taught by Singer et al (column 18, lines 1-22). In addition, it would have been obvious to the ordinary artisan that the known technique of multiplex detection using two different colored labels as taught by Singer et al could have been

applied to the method of Lea et al in view of Hansen et al with predictable results because the known technique of multiplex detection using two different colored labels as taught by Singer et al predictably results in reliable differential detection of analytes within cells.

13. Claims 102, 104, 107, and 131-132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) as applied to claim 87 above, and further in view of Riabowol (U.S. Patent No. 5,877,161, issued 2 March 1999).

It is also noted that while claim 102 has been broadly rejected as described in Section 10 above, and while claim 107 has been broadly rejected as described above in Sections 7 and 9 above, the claims are also obvious using the alternative interpretation outlined below.

Regarding claims 102, 104, 107, and 131-132, the method of claim 87 is discussed above in Section 7.

Neither Lea et al nor Hansen et al teach detection of a cell cycle related protein (i.e., claims 102 and 104); namely, cyclin D1 (i.e., claims 131-132), which is a cell cycle protein (i.e., claims 102 and 104) that is a that is a medical marker of a disease (i.e., claim 107).

However, Riabowol teaches detection of cyclin D1, which has the added advantage of allowing detection of a state of quiescence, hyperplasticity, or

neoplasia in a biological sample (column 4, lines 1-16). Thus, Riabowol teaches the know technique of detecting cyclin D1.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on cells (i.e., microparticles) as taught by Lea et al in view of Hansen et al so that the analyte detected is the cell cycle protein cyclin D1 (i.e., claims 102, 104, and 131-132), which is a marker of a disease (e.g., neoplasia; claim 107) as taught by Riabowol to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of allowing detection of a state of quiescence, hyperplasticity, or neoplasia in a biological sample as explicitly taught by Riabowol (column 4, lines 1-16). In addition, it would have been obvious to the ordinary artisan that the known technique of detecting the cell cycle protein cyclin D1 as taught by Riabowol could have been applied to the method of Lea et al in view of Hansen et al with predictable results because the known technique of detecting the cell cycle protein cyclin D1 as taught by Riabowol predictably results in reliable detection of neoplasia within cells.

14. Claims 105, 107, and 135 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) as applied to claim 87 above, and further in view of Draetta et al (U.S. Patent No 5,691,147, issued 25 November 1997).

It is noted that while claim 107 has been broadly rejected as described above in Sections 7, 8 and 12 above, the claim is also obvious using the alternative interpretation outlined below.

Regarding claims 105, 107, and 135, the method of claim 87 is discussed above in Section 7.

Neither Lea et al Hansen et al teach detection of the cell cycle related protein receptor (i.e., claim 105); namely, CDK4, which is a medical marker of a disease (i.e., claim 107) and is a cyclin dependent kinase (i.e., claim 135).

However, Draetta et al teach the detection of the level of CDK4 in a binding assay (column 25, line 65-column 26, line 35), wherein CDK4 is strongly implicated in the control of cell proliferation during the G1 phase (i.e., claims 105 and 135; column 1, lines 2-42). Determination of cell proliferation aids in the determination of the risk of certain disorders in humans (i.e., claim 107; column 3, lines 50-55). Thus, Draetta et al teach the known technique of detection CDK4.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on cells (i.e., microparticles) as taught by Lea et

al in view of Hansen et al so that the detected analyte is the a cell cycle related protein receptor CDK4 (i.e., claims 105 and 135), which is a marker of a disease (i.e., claim 107) as taught by Draetta et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of aiding in the determination of the risk of certain disorders in humans by determination of the amount of cell proliferation as explicitly taught by Draetta et al (column 1, lines 2-42 and column 3, lines 50-55). In addition, it would have been obvious to the ordinary artisan that the known technique of detecting CDK4 as taught by Draetta et al could have been applied to the method of Lea et al in view of Hansen et al with predictable results because the known technique of detecting CDK4 as taught by Draetta et al predictably results in reliable detection of certain disorders within human cells.

15. Claims 106, 107, and 136 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) as applied to claim 87 above, and further in view of Bitler et al (U.S. Patent No. 6,379,882 B1, issued 30 April 2002).

It is noted that while claim 107 has been broadly rejected as described above in Sections 7, 9, and 13-14 above, the claim is also obvious using the alternative interpretation outlined below.

Regarding claims 106, 107, and 136, the method of claim 87 is discussed above in Section 7.

Neither Lea et al nor Hansen et al teach detection of a marker of apoptosis (i.e., claim 106); namely, Annexin V (i.e., claim 136), which is a medical marker of a disease (i.e., claim 107).

However, Bitler et al teach detection of phosphatidylserines targeted with Annexin V, which has the added advantage of allowing quantitation of apoptotic cells (column 12, lines 31-54). Thus, Bitler et al teach the known technique of detection of phosphatidylserines targeted with Annexin V.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on cells (i.e., microparticles) as taught by Lea et al in view of Hansen et al so that the analyte detected is phosphatidylserines targeted with Annexin V as taught by Bitler et al to arrive at the instantly claimed invention with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of allowing quantitation of apoptotic cells as explicitly taught by Bitler et al (column 12, lines 31-54). In addition, it would have been obvious to the ordinary artisan that the known technique of detecting phosphatidylserines targeted with Annexin V as taught by Bitler et al could have been applied to the method of Lea et al in view of Hansen et al with predictable results because the known technique of

detecting phosphatidylserines targeted with Annexin V as taught by Bitler et al predictably results in reliable detection of apoptotic cells.

16. Claims 116, 118, 138, and 139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) as applied to claims 87 and 117 above, and further in view of Bobrow et al (U.S. Patent Application Publication No. US 2003/0110846 A1, published 15 August 2002).

It is noted that while claim 118 is rejected as described above in Section 7, the claim is also obvious under the alternative embodiment described below.

Regarding claims 116, 118, and 138-139, the method of claims 87 and 117 is discussed above in Section 7.

While Lea et al teach the use of fluorescent dyes, neither Lea et al nor Hansen et al teach the use of the functionally equivalent Cy-3 tyramine (i.e., claim 138), which is a cyanine derived dye (i.e., claims 118 and 139).

However, Bobrow et al teach the use of biotinyl-tyramide/streptavidin Cy3, which has the added advantage of being more sensitive that convention direct detection methods (paragraph 0033). Thus, Bobrow et al teach the known technique of using Cy3-tyramide.

It is noted that the courts have stated:

> similar properties may normally be presumed when compounds are very close in structure. Dillon, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also In re Grabiak, 769 F.2d 729, 731, 226 USPQ 870, 871 (Fed. Cir. 1985) ("When chemical compounds have very close' structural similarities and similar utilities, without more a prima facie case may be made."). Thus, evidence of similar properties or evidence of any useful properties disclosed in the prior art that would be expected to be shared by the claimed invention weighs in favor of a conclusion that the claimed invention would have been obvious. Dillon, 919 F.2d at 697-98, 16 USPQ2d at 1905; In re Wilder, 563 F.2d 457, 461, 195 USPQ 426, 430 (CCPA 1977); In re Linter, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972) (see MPEP 2144.08(d)).

Therefore, the biotinyl-tyramide/streptavidin Cy3 of Bobrow et al is an obvious variation of the claimed Cy3-tyramine.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on cells (i.e., microparticles) using a fluorescent dye as taught by Lea et al in view of Hansen et al to use the functionally equivalent obvious variant of the claimed Cy3-tryamine as taught by Bobrow et al to arrive at the instantly claimed invention with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of being more sensitive that convention direct detection methods as explicitly taught by Bobrow et al (paragraph 0033). In addition, it would have been obvious to the ordinary artisan that the known technique of using the functionally equivalent obvious variant of the claimed Cy3-tryamine as taught by Bobrow et al could have been applied to the method of Lea et al in

view of Hansen et al with predictable results because the known technique of using the functionally equivalent obvious variant of the claimed Cy3-tryamine as taught by Bobrow et al predictably results in a reliable fluorescent reporter system.

17. Claim 119 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) as applied to claim 87 above, and further in view of Mathies et al (U.S. Patent No. 6,100,535, issued 8 August 2000).

Regarding claim 119, the method of claim 87 is discussed above in Section 7.

Neither Lea et al nor Hansen et al teach the recording of the image comprises the use of a confocal scanner.

However, Mathies et al teach the use of confocal scanners, which have the added advantage of permitting high sample rates with simultaneous detection of multiple colors of fluorescent signals (column 5, lines 10-16). Thus, Mathies et al teach the known technique of using a confocal scanner.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising recording detection of analytes on cells (i.e., microparticles) as taught by Lea et al by using a confocal scanner to record the image as taught by Mathies et al to arrive at the instantly claimed method with a reasonable

expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of permitting high sample rates with simultaneous detection of multiple colors of fluorescent signals as explicitly taught by Mathies et al (column 5, lines 10-16). In addition, it would have been obvious to the ordinary artisan that the known technique of using a confocal scanner to record the image as taught by Mathies et al could have been applied to the method of Lea et al in view of Hansen et al with predictable results because the known technique of using a confocal scanner to record the image as taught by Mathies et al predictably results in reliable method of recording images.

18. Claims 102, 104-105, 107, 131, and 133 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) as applied to claim 87 above, and further in view of Sherley et al (U.S. Patent No. 5,741,646, issued 21 April 1998).

It is noted that while claim 102 is rejected as described above in Sections 9 and 13, claim 104 is rejected as described above in Section 13, claim 105 is rejected as described above in Section 14 above, claim 107 is rejected as described in Sections 7, 9, and 13-15, and claim 131 is rejected as described above in Section 13 above, the claims are also obvious using the alternate interpretation detailed below.

Regarding claims 102, 104-105, 107, 131, and 133, the method of claim 87 is discussed above in Section 7.

Neither Lea et al nor Hansen et al teach detection of p53 (i.e., claim 133), which is a tumor suppressor protein (i.e., claim 131), a cell cycle related protein (i.e., claims 102 and 104), a cell cycle related protein receptor (i.e., claim 105), and an indicator of disease (i.e., claim 107).

However, Sherley et al teach the detection of p53 (column 8, lines 40-60), wherein detection of p53 has the added advantage of aiding in the diagnosis of disease that are due to changes in cell proliferative capacity (column 2, lines 40-55). Thus, Sherley et al teach the known technique of detecting p53.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising recording detection of analytes on cells (i.e., microparticles) as taught by Lea et al in view of Hansen et al so that the analyte detected is p53 (i.e., claim 133), which is a tumor suppressor protein (i.e., claim 131), a cell cycle related protein (i.e., claims 102 and 104), a cell cycle related protein receptor (i.e., claim 105), and an indicator of disease (i.e., claim 107), as taught by Sherley et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of aiding in the diagnosis of disease that are due to changes in cell proliferative capacity as explicitly taught by Sherley et al (column 2, lines 40-55). In addition, it would have been obvious to the ordinary artisan that the known

technique of detecting p53 as taught by Sherley et al could have been applied to the method of Lea et al in view of Hansen et al with predictable results because the known technique of detecting p53 as taught by Sherley et al predictably results in detection of a molecule known to be involved in diseases caused by alteration of cellular proliferation.

19. Claims 102, 104-105, 107, and 134 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) as applied to claim 87 above, and further in view of Harvey et al (U.S. Patent No. 5,344,760, issued 6 September 1994).

It is noted that while claim 102 is rejected as described above in Sections 9, 13, and 18, claim 104 is rejected as described above in Sections 13 and 18, claim 105 is rejected as described above in Sections 14 and 18 above, and claim 107 is rejected as described in Sections 7, 9, 13-15, and 18, the claims are also obvious using the alternate interpretation detailed below.

Regarding claims 102, 104-105, 107, and 134, the method of claim 87 is discussed above in Section 7.

Neither Lea et al nor Hansen et al teach detection of epidermal growth factor receptor (i.e., claim 134), which is a cell cycle related protein (i.e., claims 102 and 104), a cell cycle related protein receptor (i.e., claim 105), and an indicator of disease (i.e., claim 107).

However, Harvey et al teach the detection of EGFR (Abstract and column 3, lines 25-40), which has the added advantage of aiding in the investigation of tumors (column 3, lines 25-50). Thus, Harvey et al teach the known technique of detecting EGFR.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising recording detection of analytes on cells (i.e., microparticles) as taught by Lea et al in view of Hansen et al so that the analyte detected is EGFR (i.e., claim 134), which is a cell cycle related protein (i.e., claims 102 and 104), a cell cycle related protein receptor (i.e., claim 105), and an indicator of disease (i.e., claim 107), as taught by Harvey et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of aiding in the investigation of tumors as explicitly taught by Harvey et al (column 3, lines 25-50). In addition, it would have been obvious to the ordinary artisan that the known technique of detecting EGFR as taught by Harvey et al could have been applied to the method of Lea et al in view of Hansen et al with predictable results because the known technique of detecting EGFR as taught by Harvey et al predictably results in detection of a molecule known to be present in tumors.

Response to Arguments

20. Applicant's arguments filed 13 March 2008 (i.e., the "Remarks") have been fully considered but they are not persuasive for the reason(s) listed below.

A. Applicant's arguments on pages 17-18 with respect to Lea et al not teaching measurement in a standstill material have been considered but are moot in view of the new ground(s) of rejection necessitated by the amendments.

It is noted, however, that contrary to Applicant's assertion that there is no suggested in Lea et al to carry out analysis on non-flowing samples, Lea et al do in fact teach that the particle stream speed should be controlled if the stream is moving too fast for accurate counting (column 3, lines 20-30), as indicated in the rejections presented above.

B. Applicant argues on pages 18-19 of the Remarks that none of the images of Lea et al captures a sufficiently strong signal to provide a high enough signal to noise ratio in each image, and that the images are unreliable an unsuitable for assessing the instantly claimed particles.

However, as noted above, Griffiths teaches detection of as little as a few hundred fluorescent molecules per bead is routine in the art (paragraph 0204). Thus, because the detection of as little as a few hundred fluorescent molecules, the artisan would, in fact, have a reasonable expectation of success in detecting low analyte numbers.

In addition, MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record" (*In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965)).

Finally, the Response above should not be construed as an invitation to file an after final declaration. See MPEP 715.09 [R-3].

C. Applicant's arguments on pages 19-20 with respect to Fan et al have been considered but are moot in view of the new ground(s) of rejection necessitated by the amendments.

D. Applicant’s arguments on pages 20-21 of the Remarks regarding the teachings of Baer et al rely on the alleged deficiencies regarding standstill imaging in the teachings of Lea et al. These arguments have been considered but are moot in view of the new ground(s) of rejection necessitated by the amendments.

E. Applicant argues on page 21 of the Remarks that the scanning laser of Baer et al cannot be relied in a completely different system (i.e., the method of Lea et al).

However, it is noted that Baer et al is not relied upon for the method of detection; rather, the prior art of Baer et al is merely relied upon for both a teaching and a motivation to assay for detection of the cell receptor CD4 as detailed above.

F. Applicant argues on page 21 that there is no expectation of success that if labeled particles are detected by one system, that the particles can be detected by another system.

However, both systems (i.e., methods of detection) are directed to the detection of fluorescently labeled analytes. Because both methods detect fluorescently labeled analytes, the ordinary artisan would have a **reasonable**

expectation of success upon combining the teachings of the prior art because all of the references have demonstrated successful detection of the fluorescently labeled analytes.

G. In response to applicant's argument on page 22 of the Remarks that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

H. Applicant argues on pages 22 and 25 that there is no expectation of success that if labeled particles are detected by one system, that the particles can be detected by another system.

However, both systems (i.e., methods of detection) are directed to the detection of fluorescently labeled analytes. Because both methods detect fluorescently labeled analytes, the ordinary artisan would have a **reasonable** expectation of success upon combining the teachings of the prior art because all of the references have demonstrated successful detection of the fluorescently labeled analytes.

I. Applicant's arguments on pages 22-23 and pages 24-25 of the Remarks regarding the teachings of Singer et al rely on the alleged deficiencies regarding standstill imaging in the teachings of Lea et al. These arguments have

been considered but are moot in view of the new ground(s) of rejection necessitated by the amendments.

J. In response to applicant's argument on page 23 and page 25 of the Remarks that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper.

K. Applicant argues on page 23 of the Remarks that Connors et al does not teach magnification below 20:1.

However, as detailed in the rejection above, Connors et al are not relied upon for the degree of magnification; rather, Connors et al is merely relied upon for both a teaching and motivation for detecting a labeling agent that binds to the nuclear membrane.

L. Applicant argues on page 23 that there is no expectation of success that if labeled particles are detected by one system, that the particles can be detected by another system.

However, both systems (i.e., methods of detection) are directed to the detection of fluorescently labeled analytes. Because both methods detect fluorescently labeled analytes, the ordinary artisan would have a **reasonable** expectation of success upon combining the teachings of the prior art because all

of the references have demonstrated successful detection of the fluorescently labeled analytes.

M. Applicant’s arguments on pages 23-24 of the Remarks regarding the teachings of Connors et al rely on the alleged deficiencies regarding standstill imaging in the teachings of Lea et al. These arguments have been considered but are moot in view of the new ground(s) of rejection necessitated by the amendments.

N. In response to applicant's argument on page 24 of the Remarks that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper.

O. Applicant's arguments on pages 25-26 with respect to Brechot et al have been considered but are moot in view of the new ground(s) of rejection necessitated by the amendments.

P. Applicant’s arguments on pages 26-27 of the Remarks regarding the teachings of Draetta et al rely on the alleged deficiencies regarding standstill imaging in the teachings of Lea et al. These arguments have been considered but are moot in view of the new ground(s) of rejection necessitated by the amendments.

Q. Applicant argues on pages 26-27 that there is no expectation of success that if labeled particles are detected by one system, that the particles can be detected by another system.

However, both systems (i.e., methods of detection) are directed to the detection of fluorescently labeled analytes. Because both methods detect fluorescently labeled analytes, the ordinary artisan would have a **reasonable** expectation of success upon combining the teachings of the prior art because all of the references have demonstrated successful detection of the fluorescently labeled analytes.

R. In response to applicant's argument on page 27 of the Remarks that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper.

S. Applicant’s arguments on pages 27 of the Remarks regarding the teachings of Bitler et al rely on the alleged deficiencies regarding standstill imaging in the teachings of Lea et al. These arguments have been considered but are moot in view of the new ground(s) of rejection necessitated by the amendments.

T. Applicant argues on pages 27-28 that the because the detection method of Mathies et al relies upon detection of bands from stained DNA

fragments, it is a measurement technique that is incompatible with the method of Lee et al and thus provides no motivation to combine the references.

However, Lea et al teach detection of fluids within a chamber in the form of an optical cell (Abstract). Mathies et al teach detection of a fluid withing a chamber in the form of a capillary (Abstract). Thus, both methods detect fluids combined within chamber. Therefore, the method are not "completely different" as asserted by Applicant on page 28 of the Remarks.

In addition, as noted above, the arguments of counsel cannot take the place of evidence in the record.

Finally, the Response above should not be construed as an invitation to file an after final declaration. See MPEP 715.09 [R-3].

V. Applicant argues on page 28 that there is no expectation of success that if labeled particles are detected by one system, that the particles can be detected by another system.

However, both systems (i.e., methods of detection) are directed to the detection of fluorescently labeled analytes. Because both methods detect fluorescently labeled analytes, the ordinary artisan would have a **reasonable** expectation of success upon combining the teachings of the prior art because all of the references have demonstrated successful detection of the fluorescently labeled analytes.

W. In response to applicant's argument on page 29 of the Remarks that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense

necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper.

X. Applicant's arguments on page 29 with respect to Yoshikawa et al ad Hart et al have been considered but are moot in view of the new ground(s) of rejection necessitated by the amendments.

Conclusion

21. No claim is allowed.

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

23. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571)272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner, Art Unit 1634

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